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Highlights

Bargain with the tooth fairy – The savings accounts for dental stem cells

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ABSTRACT

Despite the hard times COVID-19 has imposed on us, the *Biomedical Journal* strives to provide fresh and compelling reading material - to be enjoyed safely from home. In this issue, we glance behind the scenes of dental stem cell preservation for potential therapeutic use, and discover that cancer cells hijack podoplanin expression to induce thrombosis. Moreover, we learn how the helicase DDX17 promotes tumour stemness, how genetic defects in meiosis and DNA repair cause premature ovarian insufficiency, and that the brain-derived neurotrophic factor is associated with several psychiatric diseases. Further accounts relate the role of miR-95-3p in colorectal cancer, the protective power of eggplants against mercury poisoning, and the predictive value of inhibin A for premature delivery. Finally, the very rare case of adenoid cystic carcinoma in the external auditory canal receives some attention, and we get to read up on how 3D imaging and modelling combines functional and aesthetic repair of cleft lip and palate cases.

Spotlight on reviews

Bargain with the tooth fairy – the saving accounts for dental stem cells

There is a clear linguistic split in Europe and the Americas, regarding the belief in supernatural entities who are in charge of baby teeth retrieval in exchange for cash.

Scandinavian countries, where the myth probably originated, as well as Slavic and Germanic-language nations rely on the tooth fairy,¹ whereas countries with Romance languages outsourced the job to a mouse, sometimes just referred to as the “little mouse” (France), or “the mouse Pérez”

(Hispanic countries). In all cases, the tooth has to be placed under the pillow before going to sleep and will have been traded for money by the next morning. Asian beliefs focus more on the future of the adult tooth to come: in China for instance, a baby tooth from the upper jaw has to be thrown under the bed or buried, and one from the lower jaw thrown onto the roof, for the new tooth to grow quickly and straight into the right direction.² Funnily enough, mice are an exception among mammals, as they are monophyodonts and thus do normally not shed any teeth, which has made them an interesting model to investigate the evolution of replacement teeth [1]. Mammals for their part are the exception among vertebrates, which are usually polyphyodonts, meaning that

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¹ Occasionally a troll, at least in Finland.

² Based on a personal survey.

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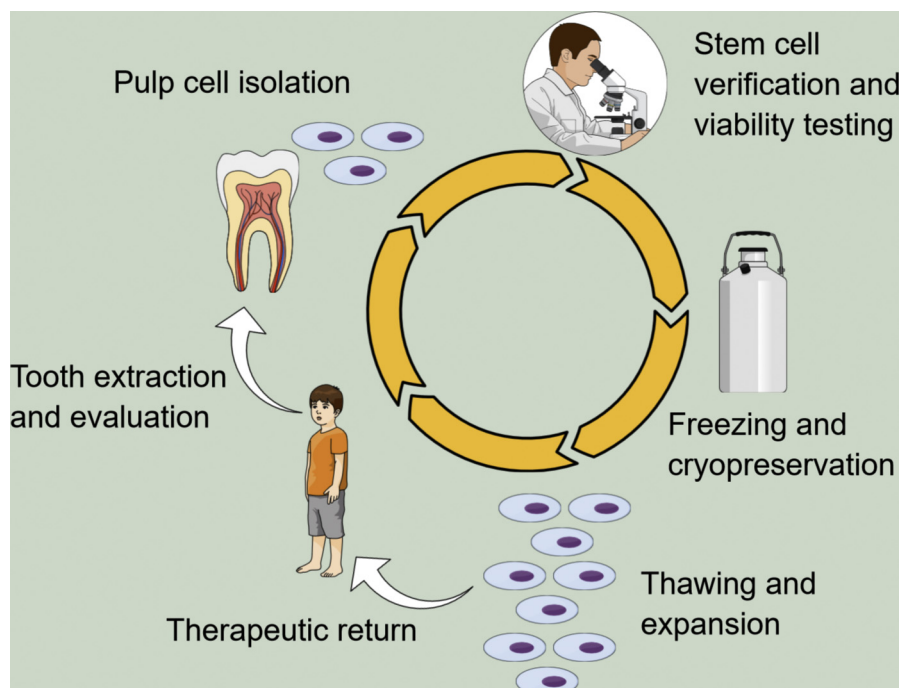


Fig. 1 The main steps of dental pulp stem cell preservation for potential later therapeutic use. Various companies offer the isolation of dental pulp stem cells from deciduous or adult teeth, followed by expansion, quality control and cryopreservation for an extended period of time. The expected use would be autologous tissue repair in the oral cavity, and eventually regeneration of other tissues depending on technical and technological advancements. Figure kindly provided by Zeitlin et al. [3]. See main article for details.

they can regrow a practically unlimited supply of replacement teeth all throughout their lifetime [2]. Hence, humans possess a more complex, but only diphyodont dentition: a trial version of deciduous teeth, replaced around age 6 by a permanent set. Loss of any component of the latter, through mechanical injury, infection, or age entails the need for artificial replacement, and usually steep medical bills.

In these circumstances, Zeitlin et al. present a refreshing account about companies offering the extraction, expansion, and preservation of dental stem cells, highlighting scientific facts, clinical evidence, and the practicalities of the service [3].

The authors start with a comprehensive overview of the hierarchy of stem cells, from totipotent – capable of generating all embryonic and extraembryonic tissues – to multipotent, also known as adult stem cells (ASCs), a heterogeneous group of cells with a limited potential to proliferate and to give rise to several cell types of a given organ.

Without doubt, it is the discovery of induced pluripotent stem cells (iPSCs) in 2006 that mainly triggered massive hopes for autologous tissue repair [4]. After all, the theory sounds as straightforward as alluring, given that terminally differentiated cells can be reprogrammed to an embryonic stem cell-like state, and subsequently differentiated into the needed cell type. As it turned out however, the official availability of this kind of technology might take some time [5].

Somehow, ASCs inherited these therapeutic hopes, and without delay, businesses sprang to life, offering the storage of precious potential replacement parts. Given that both the amount and the differentiation potential of ASCs seem to decline with age [6], the trend is to harvest the earliest

available cell material with the largest differentiation spectrum. The prime examples are haematopoietic stem cells and mesenchymal stem cells (MSCs) derived from the umbilical cord [7,8]. Notably the latter are currently used in countless clinical trials [9], and kicked off the *tissue cryobanking* business. As a consequence, in 2018, over 450 companies worldwide offered cord blood banking services.³ Securing this cell source however is possible only during an extremely short time window and relies on the individual's parents' sole decision. Therefore, more and more alternative ASC sources have been explored over the recent years. A good example was discussed in a recent issue of the *Biomedical Journal*, where we discovered the promising potential of locally derived MSCs derived for the repair of anterior cruciate ligaments [10,11].

Here, the authors acquaint the reader with the different classes of ASCs found in the oral cavity: in a nutshell, the two main ones are derived from the dental pulp of either baby teeth, bound to be shed anyways, or adult teeth, accessible for example after wisdom tooth removal.

One very interesting feature of dental pulp stem cells is that they originate from the neural crest, itself of ectodermal origin. Neural crest cells are a fascinating ingredient of embryogenesis, in view of their unique ability to migrate into almost any tissue, and to participate in its development [12], and species-specific pattern [13]. In the current context, they

³ <https://www.globenewswire.com/news-release/2018/10/18/1623156/0/en/Global-Cord-Blood-Banking-Industry-Report-2018-Approximately-450-Companies-Offering-Cord-Blood-Banking-Services-Worldwide.html>.

serve as a reminder of the heterogeneous nature of MSCs, which can derive from two different embryonic germ layers - mesoderm and ectoderm - and explain why dental pulp stem cells can give rise to functional neurons [14].

Importantly, Zeitlin and colleagues point out the discrepancy between the exuberant promises featured by the internet regarding the therapeutic potential of dental pulp stem cells, and the available clinical evidence. Admittedly, the cells flirt with the pluripotent end of the ASC spectrum, as they have given rise to derivatives of all three embryonic germ layers in a chaotic manner *in vitro* or as teratomas, and could be directed into the typical progeny of MSCs plus neurons and odontoblasts [15]. Nonetheless, the authors estimate that their best chances for concrete use will be the direct repair of specific dental lesions or the indirect improvement of tissue regeneration through immunomodulation [16].

The second part of the review details the practical process of tooth banking, a service offered by at least 15 companies (Fig. 1). After a frankly entertaining section dedicated to various recommended storage options for tooth transport, from cow milk to sports drinks, the authors speculate on the most likely protocols for stem cell isolation. The two main possibilities are mechano-enzymatic dissociation into single cell populations and tissue outgrowth, with the latter maybe reminding the reader of one early and original way of reprogramming keratinocytes from plucked hair directly in a dish [17]. Tests for viability and pluripotency can vary between companies, while there is little doubt on the efficiency of common freezing protocols, preservation in liquid nitrogen, and finally the possibility to recover functional cells after prolonged freezing.

Remains the obvious debate of the cost aspect. Or rather, the financial investment *versus* the realism degree of the promised benefits. From this point of view, tooth banking might be the safe certificates of deposit on the human body parts stock market, especially when compared to much more eccentric options: about six different companies, most of them located in the United States, offer the cryogenic preservation of either the entire body or the severed head after the client has been declared clinically dead, for a modest fee ranging from \$28 000 to \$200 000, and absolute faith into some distant future technologies to reanimate them.⁴ Although the idea is resourcefully described as an “ambulance through time” by the director of one institute,⁵ neither the fields of science nor economy grant it any support - the first because of the massive damage current cryopreservation does notably to the brain, the second based on the fact that companies very rarely survive more than a hundred years.

Determined to counter at least the first factor, the company Nectome founded in 2018 (and not a *Black Mirror* episode) opted for the life-incompatible but near-atomic, chemical preservation of the brain through cross-linking, assuming that the distant future technologies will be able to scan the

structure and infer all necessary information to simulate the late individual, memories included.

Clearly, fiction has come a long way since the tooth fairy - yet the latter seems still the more reliable ally when it comes to tissue replacement.

Spotlight on original articles

Sticking together – how cancer cells manipulate platelet aggregation

Not only do tumour cells hijack countless intracellular cell signalling pathways, but they equally ensnare their surroundings, coaxing their microenvironment into a suitable, supportive niche [18], and exerting long-range influence on the remaining organism by shedding vesicles into the circulation [19]. On these grounds, the collection of molecules displayed on the surface of cancer cells is of particular interest, evidently in order to recognise and target them [20], but also to understand how they communicate with neighbouring cells and escape the immune system [19]. Multiple components of the cancer cell surface have already been thoroughly investigated, such as the glycocalyx [21], integrins [22], and cell surface receptors [23].

Lee et al. have set their sights on podoplanin (PDPN) [24], a transmembrane mucin-like glycoprotein required for the correct development of lung alveoli, heart, and lymphatic system, to cite only a few functions [25]. The major particularity of PDPN though is that it does not possess any functional domains or enzymatic activities on its own. Instead, it exerts its “activities” by interacting with numerous molecules present either on the same cell surface as PDPN, or on neighbouring cells. Examples include the C-type lectin-like receptor-2 (CLEC-2), CD44, or protein kinase A (PKA) [26]. In particular, activation of CLEC-2 by PDPN on lymphatic endothelial cells or fibroblastic reticular cells triggers platelet activation and aggregation, which is necessary for the accurate separation of blood and lymphatic vessels [27], and cerebrovascular patterning [28].

Once development achieved, PDPN probably participates in the maintenance of endothelial integrity [27], but is also frequently upregulated on tumour cells, or on immune cells, fibroblasts, and epithelial cells during inflammation [25]. In the cancer setting, PDPN is said to promote migration, invasion, metastasis, proliferation, and clonal capacity [25,26], yet the underlying mechanisms are forcefully dependent on its binding partners. Notably, little is known about PDPN's ability to induce platelet aggregation in a tumour context.

Lee et al. concentrate here on oral squamous cell carcinoma (OSCC), a highly lethal cancer type with over 300 000 new cases per year and 50% of patients dying within 5 years [29]. The authors confirm the expression of PDPN in five out of nine OSCC cell lines, before focusing on the commonly used OECM-1 line. One interesting observation is that the average PDPN levels are not due to a homogeneous expression, but that the cell population can be further separated into P+ cells with high and P- with low or absent PDPN levels. This immediately echoes the frequent detection of cellular heterogeneity within the same tumour, with stem cell-like

⁴ <http://reillytop10.com/previous-lists/2017-list/reanimating-cryonics/>.

⁵ <https://www.youtube.com/watch?v=zRxI0DaQrag&feature=youtu.be&t=1034>.

tumour initiating subpopulations as the most intensely researched - and controversial - case [30].

Stable and efficient knock-down by small hairpin RNAs (shRNA) of PDPN is subsequently achieved in the P+ fraction, with no impact on cell morphology, and surprisingly also no alteration of cell proliferation, in contrast to some previous reports [25,26]. Nevertheless, as PDPN function depends on its interaction partners, substantial differences in phenotypes could be due to different triggered pathways.

Unlike the absence of an effect on proliferation however, the knock-down of PDPN significantly reduces *in vitro* invasion and migration abilities, in accordance with other studies. Aggregation of human washed platelets was only observed after substantial overexpression of PDPN in P+ cells, raising again the question if other factors are required for the molecule to deploy its full potential, especially as aggregation takes place with platelet and cancer cells, and is inhibited by PDPN knock-down. In due course, the authors turn *in vivo*, using a real-time monitored ectopic xenograft model in immunocompromised mice. The previous observation that PDPN expression does not have an effect on proliferation holds true in the mouse model, as knock-down of the protein in P+ cells does not change tumour growth and metastasis compared to the mock shRNA. Nonetheless, survival is considerably shortened in the control compared to mice injected with PDPN knock-down cells. Notably, these animals showed platelet infiltration into the primary tumour, intravascular platelet aggregation, and presented multiple signs of increased intravascular thrombosis activity.

Finally, the authors replicate most of the previous results, this time by overexpressing PDPN in the P- population. The high-level PDPN cells induce platelet aggregation *in vitro*, shorten the survival of mice in a xenograft model, and lead to platelet accumulation inside the tumour and blood vessels. However, no significant increase in thrombosis markers is noted, leading once again to the possibility that an unknown co-factor modulates PDPN function. Lee et al. hypothesise as a matter of fact that the P+ and P- subpopulations differ in more ways than their PDPN expression levels, and that the P- fraction lacks the partner required for PDPN to trigger coagulation.

The downstream effects of PDPN-mediated thrombosis are not clear yet. One could speculate though that platelet aggregation would facilitate the slowing down of circulating tumour cells (CTCs), and their subsequent extravasation and invasion of distant tissues. Lee et al. did not observe a correlation of metastasis and PDPN in their specific setting, but as the field of CTC biology is only in its beginnings – see the previous issue of the *Biomedical Journal* [31,32] – the hypothesis certainly deserves further investigation.

Also in this issue

Reviews

Back to the origins - hypoxia shifts DDX17 function from miRNA biogenesis to promoting cancer stemness

Cancer stem cells (CSCs) are the controversial and dreaded joker card of any tumour, as they are held responsible for augmented growth, invasion, resistance to treatment, and

finally relapse after seemingly successful eradication of the primary tumour [33].

Through high-jacking of the organism's normally tightly controlled pluripotency pathways, cancer cells acquire properties such as immortality, high proliferation rates, and increased resistance to damage or harsh environments, such as hypoxia. Moreover, stemness gain is also associated with epithelial mesenchymal transition, and thus increased cell mobility and invasion properties [34]. All components of the pluripotency pathways have been found to be misappropriated by cancer, including proteins, long noncoding RNAs [35], and of course microRNAs (miRNAs).

Kou-Juey Wu dedicates a detailed review to an extremely polyvalent component of miRNA biogenesis and regulation, the microprocessor cofactor DEAD-box helicase 17 (DDX17), and its implication in promoting cancer stemness under hypoxic conditions [36]. The author elaborates on the CSC concept and recapitulates the essentials of miRNA biogenesis, regulation, and the established connection between miRNA deregulation and tumorigenesis, as well as the many roles of DDX17 in all of these. Subsequently, it is explained how hypoxia shifts the DDX17 activity by K63-linked polyubiquitination from cytoplasmic miRNA biogenesis to various nuclear functions. This decreases the production of anti-stemness miRNAs, while increasing the expression of pluripotency factors, as DDX17 features as a transcription cofactor and promotes activating epigenetic changes.

Fair share – how defective meiosis and DNA repair cause female infertility

Accurate cell division and distribution of genetic information is rather important for any cell type, for germ cells however, specifically undergoing meiosis, it is a matter of life and death [37]. Therefore, it does not come as a surprise that defects of the meiotic apparatus and DNA repair systematically lead to infertility. These shortcomings can be caused by pathogens, autoimmune diseases, environmental factors, or have a genetic base [38].

In his review, Reiner Veitia focuses on how mutations affecting genes involved in meiosis and DNA repair can lead to premature ovarian insufficiency (POI), one of the principal causes of female infertility [39]. Stressing the powerful combination of high throughput sequencing with classical genetics in consanguineous families, the author provides and exhaustive description of genetic variants connecting POI and meiotic chromosome pairing, as well as DNA recombination and repair.

Minds and molecules – associations of BDNF with mental disorders

Deciphering the underlying molecular causes of psychiatric disorders is an ongoing Herculean task, given the heterogeneity of the disorder spectra, just as much as the multifactorial nature of their causes, embracing genetics, epigenetics and environment. High throughput –omics, from transcriptomics to metabolomics, were expected to shed some light onto the matter, and have definitively delivered some clues, yet high-dimensionality data analytics on huge datasets are required in order to take into account the complexity of the system [40].

The implication of Brain-Derived Neurotrophic Factor (BDNF) in psychiatric diseases can be considered an educated guess, given the importance of the protein in countless developmental and functional processes of the mammalian brain [41].

Here, Lin and Huang have compiled a comprehensive selection of studies relating the possible connection of BDNF with schizophrenia, major depressive disorder, and bipolar disorder [42]. They thoroughly discuss associations with either protein or mRNA abundance, single nucleotide polymorphisms, or epigenetic modifications of the BDNF locus, and stress at the occasion the importance of additional patient stratification by gender, ethnicity, disease stage or phase, and physiological components.

Original articles

Janus-faced small molecules - miR-95-39 acts as a tumour suppressor in colorectal cancer

Literature on microRNAs (miRNAs) levels as highly specific biomarkers and therapeutic targets for all cancer types has recently exploded [43,44], and several miRNA replacement therapies are currently at clinical trial stages [45]. Nonetheless, just as much as different cancer types display highly divergent properties, and strong heterogeneity even among the same tumour class, the role of a certain miRNA can be contrasting depending on the context.

MiR-95-3p has already been studied in many cancers, and been found to act either as an oncogene [46], or as a tumour suppressor [47], depending on the dominant mechanism. Hong et al. extend the list by investigating here the role of miR-95-3p in colorectal cancer (CRC) [48]. The authors show that miR-95-3p expression is lower in CRC cell lines and tumour tissue compared to normal intestinal cells or adjacent tissue. Moreover, patients with the lowest miR-95-3p expression levels displayed worse recurrence survival and overall survival rates. Overexpression of miR-95-3p inhibited cell proliferation and mobility of CRC cells *in vitro*, as well as tumour growth and metastasis in a mouse xenograft model, and improved the survival of the latter. The hepatoma-derived growth factor (HDGF) was identified *in silico* as a putative target for miR-95-3p, and subsequently validated by several assays. According to these results, miR-95-3p qualifies as a tumour suppressor in CRC, and could be a reliable prognostic biomarker from early stages on, while HDGF might represent a therapeutic target.

Eat your vegetables – eggplant extract reduces mercury chloride toxicity in testes

The expression “to be mad as a hatter” potentially stems from the symptoms of mercury poisoning, as mercuric nitrate was routinely used to separate the fur from the pelt in the felt hatting industry [49]. The curious, liquid metal, commonly known as quicksilver, was used during centuries for medicinal and industrial applications, from magico-religious rituals to metal recovery processes, or to treat syphilis [50]. It took quite some time to recognise the highly harmful effects of mercury,

notably on the nervous system [51] - as proven by Minamata disease, the neurological disorder caused by methylmercury released into the industrial wastewater by the Japanese Chisso chemical factory until 1968 [52]. Nowadays, the main sources of human exposure are dental amalgams, occupational exposure, or contaminated fish [53]. Eggplants, on the opposite, are not only delicious on pizza, but fully loaded with health benefits in the form of vitamins, phenolics and antioxidants [54]. Moreover, as shown here by Adelakun et al., feeding rats whole eggplant extract in parallel with mercury chloride reduces significantly the testicular toxicity of the latter by boosting the organism's antioxidant system [55].

Early warnings for early babies – inhibin A could be used as a marker for preterm birth risk

Preterm birth (PTB) designates delivery earlier than 37 weeks of gestation and is the leading cause of neonatal death and a major risk factor for death before age 5, as well as developmental disabilities [56]. Early detection of preterm labour is key for adequate prevention and management, however, the underlying causes are complex and multi-factorial. Known risk factors encompass infections, stress, multiple gestations, or maternal body weight - yet about two-thirds of PTB cases lack an apparent predisposition [57]. Measurement of cervical length is so far one of the most reliable and cost-effective methods [58], but over the past decade, much effort was made to additionally identify biomarkers predictive of spontaneous PTB in maternal blood at earlier stages [59,60]. Until now, it has been considered quite unlikely that a single test would be sufficient for predicting PTB [61], however data gathered by Huang and colleagues strongly indicate that maternal inhibin A levels from the second trimester are a good candidate [62]. Inhibin is a glycoprotein and probably named during a peak moment of pragmatism, as it inhibits follicle-stimulating hormone (FSH) secretion, in unsurprising contrast to activin [63]. So far, it has been used as a biomarker for ovarian cancer [64] and Down syndrome [65]. Huang et al. show here that inhibin A levels over 2.25 are statistically significant in their association with preterm labour [62], and might thus be an early clue prompting closer monitoring of the patients.

Don't turn a deaf ear to adenoid cystic carcinoma in the external auditory canal

Adenoid cystic carcinoma (ACC) is a rare form of cancer with an approximate incidence rate of 0.4 per 100 000, a preference for salivary glands and female individuals, and a tendency to spread alongside nerve tracts. Moreover, its slow but steady growth delays diagnosis and comes along with frequent recurrence and metastasis, reducing by half the survival rates between 5 and 15 years.⁶ ACC occurring in the external auditory canal (EAC) ranges about four orders of magnitude under ACC incidence, that is to say that information is sparse, misdiagnosis frequent, and a treatment consensus absent [66,67].

Chen et al. decided to improve the limited amount of available information with a retrospective review on twelve

⁶ <https://www.accoi.org/faq/acc-statistics/>.

EAC AAC patients over 30 years from a single institution in Taiwan, describing patient characteristics, symptoms, treatments and outcomes. In conclusion, they advise to include EAC AAC as a possible diagnostic for middle-aged women with lasting ear pain and an EAC mass, as well as to closely monitor the appearance of lung metastases [68].

News and Perspectives

Help for Oddjob⁷ – fixing form and function by orthognathic surgery of cleft lip and palate

The craniofacial development of the human embryo is a highly complex process that takes place mainly during the first trimester, and requires the correct formation and fusion of five primitive tissue lobes [69]. Numerous genetic defects and environmental factors can lead to defaults in the final fusion steps, leading among others to a cleft lip and/or palate. Besides problems with feeding, dental occlusion, speech and infections, the condition entails a heavy psychosocial burden, exemplified by the severely biased depiction of individuals with an orofacial cleft as villains in works of fiction.⁸ Early surgery usually achieves the re-establishment of functional features and satisfying facial aesthetics. Nevertheless, both goals can sometimes be conflicting. Multiple articles in the recent issues of the *Biomedical Journal* have illustrated that the patient's pre- and post-operative opinion and satisfaction are more and more considered for orthognathic surgery [70,71]. Hence, Denadai et al. explain in this issue's editorial note how three-dimensional imaging and computer-aided modelling of the surgery outcome, in combination with the taking into consideration of the patient's, or patient's family's, preferences has improved the outcome of orthognathic orofacial cleft surgery both in terms of functional and aesthetic outcome [72].

Conflicts of interest

The author declares no conflict of interests.

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To all these among my social network, who enthusiastically answered my survey about milk teeth related traditions.

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⁷ A secondary villain character from the James Bond – Goldfinger novel and movie.

⁸ https://www.academia.edu/2385198/The_Monster_Without_Red_Dragon_the_Cleft-Lip_and_the_Politics_of_Recognition.

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